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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/904,536	07/16/2001	Thomas J. Graddis	3260.0028-01	3851

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EXAMINER

SPECTOR, LORRAINE

ART UNIT	PAPER NUMBER
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1647

DATE MAILED: 10/14/2003

10

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/904,536

Applicant(s)

GRADDIS ET AL.

Examiner

Lorraine Spector, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 July 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 33-45, 52-55 and 69-110 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 33-45, 52-55 and 69-110 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

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Part III: Detailed Office Action

Claims 33-45 and 52-55, and newly introduced claims 69-110 are pending.

The previous rejections under 35 U.S.C. §112, and §102 have been overcome by amendment.

New rejections apply.

Formal Matters:

The new title of the invention is acknowledged.

The claims are now largely commensurate in scope with the claims allowed in the parent application, now U.S. Patent Number 6,291,661 B1 with the exception that the issued patent recites that the claimed proteins must have increased or decreased activity relative to wild-type Flt-3 ligand, a limitation absent from the pending claims.

Objections and Rejections under 35 U.S.C. §112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 74, 80, 88, 96, 104 and 110 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite because they require that the protein being used both comprise a given sequence and at the same time differ from that same sequence. Unless applicants intend that there are two copies of the sequence present, one wild-type and one mutated, both cannot simultaneously occur.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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Claims 33-45, 52-55 and 69-110 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to:

1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is that applicants have invented various muteins of flt3-ligand. The disclosed muteins have various activities, some having no activity at all, some having increased activity, some having decreased activity. For example, the specification discloses that mutations selected from the group consisting of S9G, F15Y, R20C, R55C, R55L, A64T, V75A, F81L, P90S, R95C AND F124L all have activity which is decreased by at least 40% but is not essentially zero, and those selected from L3H, H8Y, K84E, K84T, W118R or Q122R, or multiple mutants K84E/Q122R and L-3H/H8Y/K84E/Q122R all have activity which is increased by at least 40%. It is noted that different substitutions at a single site can have different effects, as discussed in more detail below. Numerous muteins had no detectable activity. The specification teaches that the proteins may be used for stimulation of cell expansion. Both muteins with increased and decreased activity are disclosed, as are non-functional muteins.

The breadth of the claims is such that no specific activity (increase or decreased relative to wild-type, or totally inactive) is required by the claims. Although the medical conditions to be treated, such as those in claim 45, find *in ipsius verbis* support in the specification, there is not guidance as to what the desired activity of the protein to be administered would be; e.g. whether applicants intend an agonist or an antagonist to be administered. While it is clear that muteins with increased activity could be used, for example, for *in vitro* cell expansion of hematopoietic cells, the claims have no functional limitations as to the protein being used. The specification

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does not provide guidance in the use of muteins having reduced or absent activity, and provides no specific guidance nor working example for any of the specifically recited conditions. It is especially noted that claim 44 encompasses the treatment of both conditions resulting from a hyperactive or inappropriate immune response (allergy, autoimmunity), as well as conditions that are characterized by an inadequate immune response (immunosuppression). The specification simply does not provide guidance as to which of the numerous species encompassed by the claims are to be used for which conditions, and in what manner.

The specification presents a large amount of data pertaining to the results of a random mutagenesis. While the instant specification presents characterization of several mutants, examination of the data therein point out the unpredictability of particular substitutions. For example, it is noted that mutation H8R (a basic for a basic amino acid, which is a conservative substitution) was inactive, whereas H8Y (an aromatic amino acid for a basic amino acid, a non-conservative substitution) had 1.7x wild type activity. This demonstrates that even when a particular mutation is identified, it is not predictable what would be the activity of other mutations at the same locus. Similarly, results at one residue cannot be extrapolated to surrounding residues, as evidenced by mutants L26F and L27P. Even if the *general* effect of mutations could be predicted, it cannot be predicted what the actual activity of the mutants would be. The specification itself evidences the unpredictability of altering the protein; a mutation at a given residue is not predictive of the effect of mutations at adjoining residues, and wherein a mutation at a given residue is not even predictive of the effect of a different mutation at the same residues. Further, even claims that recite particular mutations are not limited to such, due to the use of "comprising" language, and the effects of multiple mutations within a single protein are not predictable. Thus, while the specification enables the use of particular muteins cited above which have increased activity, for some applications, such as the induction of cellular expansion, enablement is not commensurate with the broad scope of the claims. The art of record does not teach the use or administration of Flt3-L muteins meeting the claim limitations for any purpose, nor does it teach the use of muteins having reduced or absent activity for any purpose.

Accordingly, in view of the lack of functional limitations in the claims, the breadth of the muteins that may be used in the claimed methods, the lack of teachings as to the properties of particular muteins, and the lack of guidance or working examples as to which muteins should be

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used in what circumstances (or desirable activity levels of such muteins), the Examiner concludes that it would require undue experimentation to practice the claimed invention in a manner commensurate in scope with the claims, and hence that enablement is not commensurate in scope with the claims.

Advisory Information:

No claim is allowed.

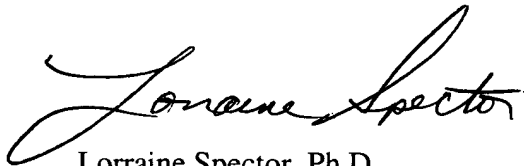
Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 5:30 P.M.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary L. Kunz, at (703)308-4623.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 872-9306 (before final rejection) or (703)872-9307 (after final). Faxed draft or informal communications with the examiner should be directed to (703) 746-5228.

A handwritten signature in cursive script that reads "Lorraine Spector". The signature is written in dark ink and is positioned above the printed name and title.

Lorraine Spector, Ph.D.
Primary Examiner